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THERMAL STUDY OF CEFOPERAZONE MONOHYDRATE

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Cefoperazone is a third generation cephalosporin antibiotic. In the present work, the thermal decomposition processes of this cephalosporin were investigated using TG and DTG techniques. Arguments for a rapid thermooxidation of the molecule were brought by EGA by identifying the substances which arise from both the destruction of radicals and the destruction dihydrothiazine cycle. It was identifying three stages of decomposition: dehydration process; degradation of dihydrothiazine ring, respectively further decomposition with releasing of phenol, azine and N-ethyl-formamide from the substituents.

INTRODUCTION

The vast pharmaceutical and biological implications of β-lactam antibiotics have promoted a large number of studies on their chemical reactions. The introduction of a variety of substituents at different positions of the cephalosporin nucleus has generated a vast array of compounds with differences in the spectra of activity and in various properties such as a better oral availability, stability to hydrolysis by β-lactamases, protein binding affinities, and various other chemical susceptibilities.[1–3]

Cefoperazone is a third generation cephalosporin antibiotic. It is one of few cephalosporin antibiotics effective in treating Pseudomonas bacterial infections which are otherwise resistant to these antibiotics. Cefoperazone exerts its bactericidal effect by inhibiting the bacterial cell wall synthesis.[4,5]

Thermal methods of analysis are widely used for investigation of the thermal decomposition of organic compounds.[6–8] These studies play an important role in the development of compounds, which are commonly used by manufacturers of rugs, cosmetics, and other products of the chemical industry. Generally, the thermal stability of an organic compound depends not only on the chemical structure but on the particle size, the degree of crystalline, the purity, temperature of storage and the surrounding gas atmosphere as well. [9–12] A series of works, even recent ones, show encouraging results regarding the evaluation of the thermal behaviour of pharmaceutical products through the kinetic data obtained in non–isothermal conditions.[13–16]

Thermogravimetric analysis (TG) provides information regarding mass changes in the sample resulting from heat treatment under controlled environment. However, it does not provide any chemical information regarding the gases evolved during the thermal degradation. Using FT-IR spectrometry in combination with TG, it is often possible to identify the evolved gases, and also monitor their evolution profiles during thermal degradation.[17]

In order to elucidate the basic reactions of thermal degradation of cefoperazone itself in oxidative atmosphere, here we present our study on identification and tracing of evolving gaseous species from pure cefoperazone monohydrate using coupled FTIR spectrometric gas cell as

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detector connected to furnaces of thermal balances (TG–FTIR). The components of released gaseous mixtures have been monitored and identified mostly on the basis of their FTIR spectra.

Cefoperazone's formula is presented in Fig. 1.

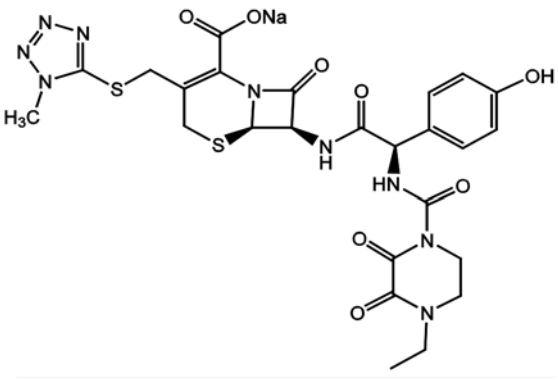


Fig. 1 – The chemical structure of the cefoperazone.

RESULTS AND DISCUSSION

a) Thermal Behaviour

One of the thermal curves of this active substance, obtained under dynamic temperature conditions is presented in Fig. 2.

The thermal analysis results of cefoperazone monohydrate, register in non-isothermal conditions, at different heating rates, are summarized in Table 1.

From the curves TG / DTG presented in Fig.2 it comes out that the active substance presents a reduced thermal stability, beginning with a ≈ 40ºC temperature. The decomposition occurs through several stages which are difficult to be separated from thermogravimetric curve. So, the first decomposition stage takes place with a loss of approximately 6.94% which corresponds to water being eliminated from cefoperazone monohydrate composition, the second stage takes place with 7.02% loss, respectively the third stage has a 23.97% loss.

On the DTA curve, it can be observed an endothermic transformation between 36–150°C (dehydration process), respectively two transformations with their peaks at 196°C and 243°C (the active substance decomposition). The last two processes are strongly of exothermic nature.

b) EGA results

From Gram-Schmidt profile and thermogravimetric curves recorded at a heating rate β = 20°C/min, shown in Fig.3, respectively Fig.4, it is observed that the maximum peak occurs after about 10 minutes, the DTG curve's maximum was recorded at a temperature of 210°C, in that moment ***t*** the maximum concentration of the gases has been met. At this point, the EGA spectrum it sets out for cefoperazone (Fig. 5).

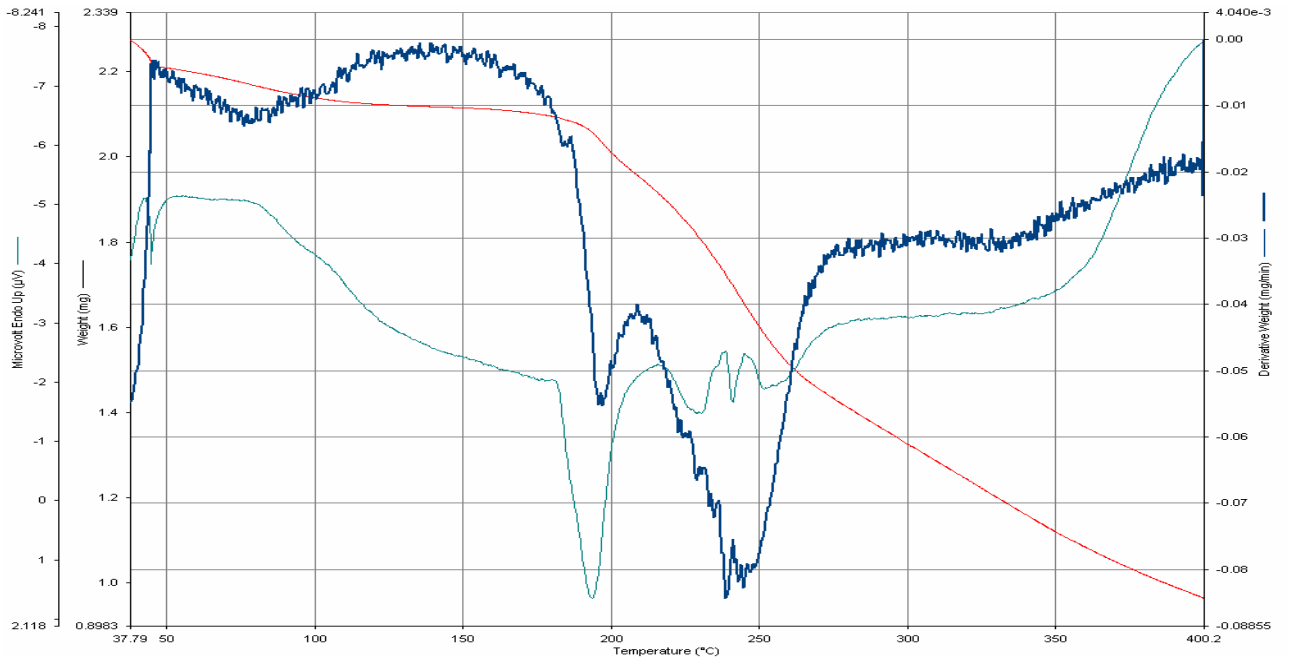


Fig. 2 – The thermoanalytical curves TG / DTG / DTA obtained in air at heating rate of 7°C·min^{-1} for cefoperazone monohydrate – active substance.

Table 1

Thermoanalytical data of cefoperazone monohydrate – active substance, at different heating rate

β (°C/min)	Process	T_i (°C)	T_f (°C)	$T_{max\ DTG}$ (°C)	$T_{max\ DTA}$ (°C)	Thermal effect	Δm (%)
5	I	50	150	70		endothermic	7.048
	II	170	210	195	190	exothermic	7.661
	III	210	260	240	220	exothermic	24.004
7	I	50	120	75		endothermic	6.936
	II	150	210	195	190	exothermic	7.024
	III	210	274	245	230	exothermic	23.968
10	I	50	150	70	65	endothermic	7.034
	II	150	215	201	198	exothermic	6.448
	III	215	300	245	240	exothermic	27.902
12	I	50	150	80	75	endothermic	6.875
	II	150	220	201	199	exothermic	7.673
	III	220	254	235	255	exothermic	24.959

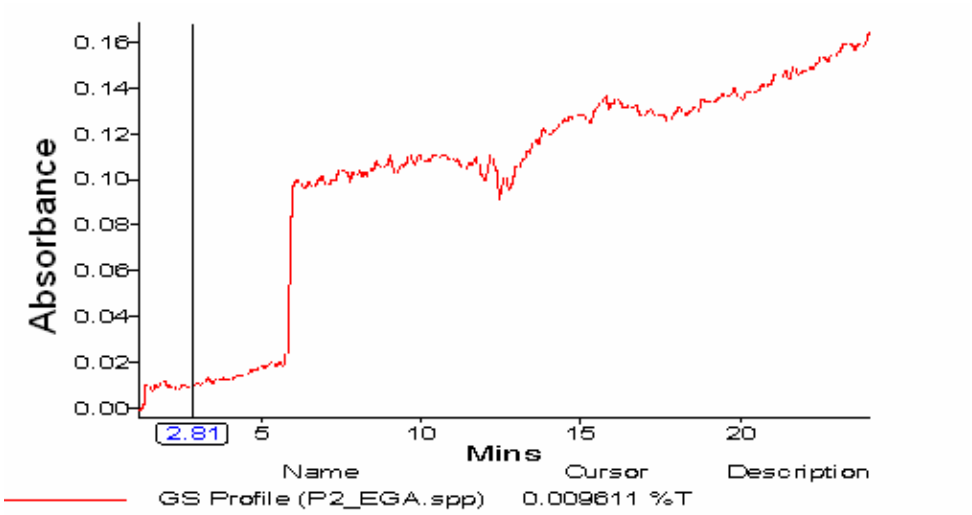


Fig. 3 – Gram–Schmidt profile for cefoperazone monohydrate (β=20 grades/minutes).

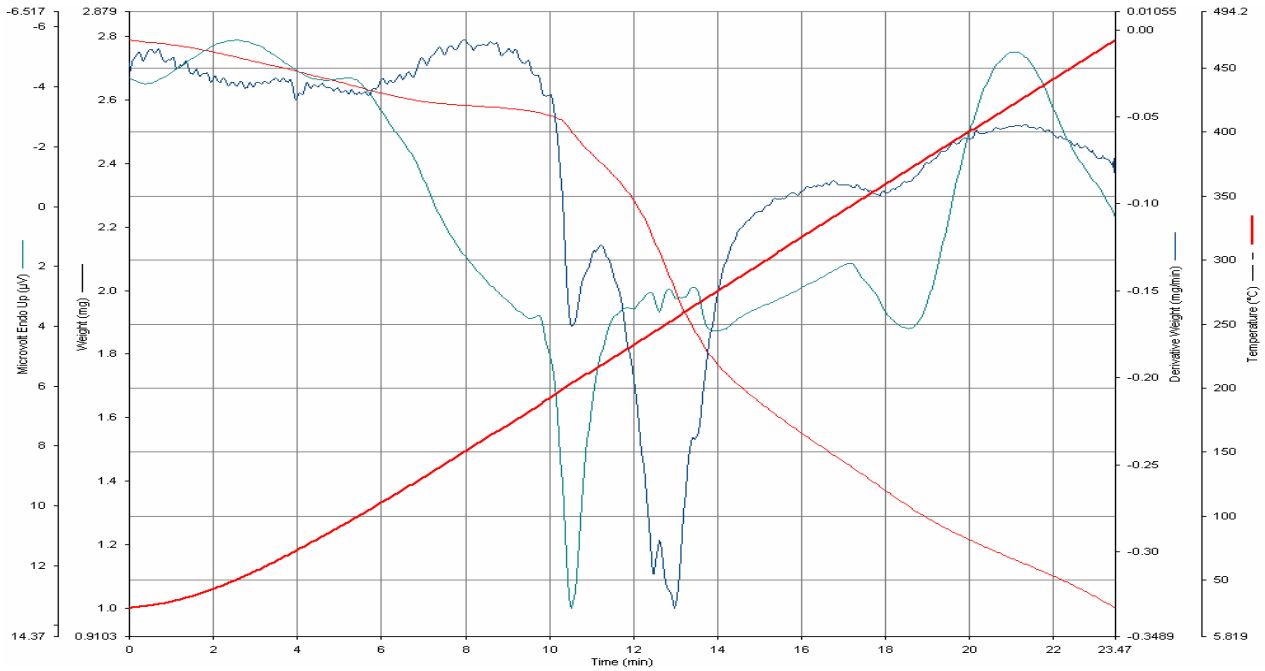
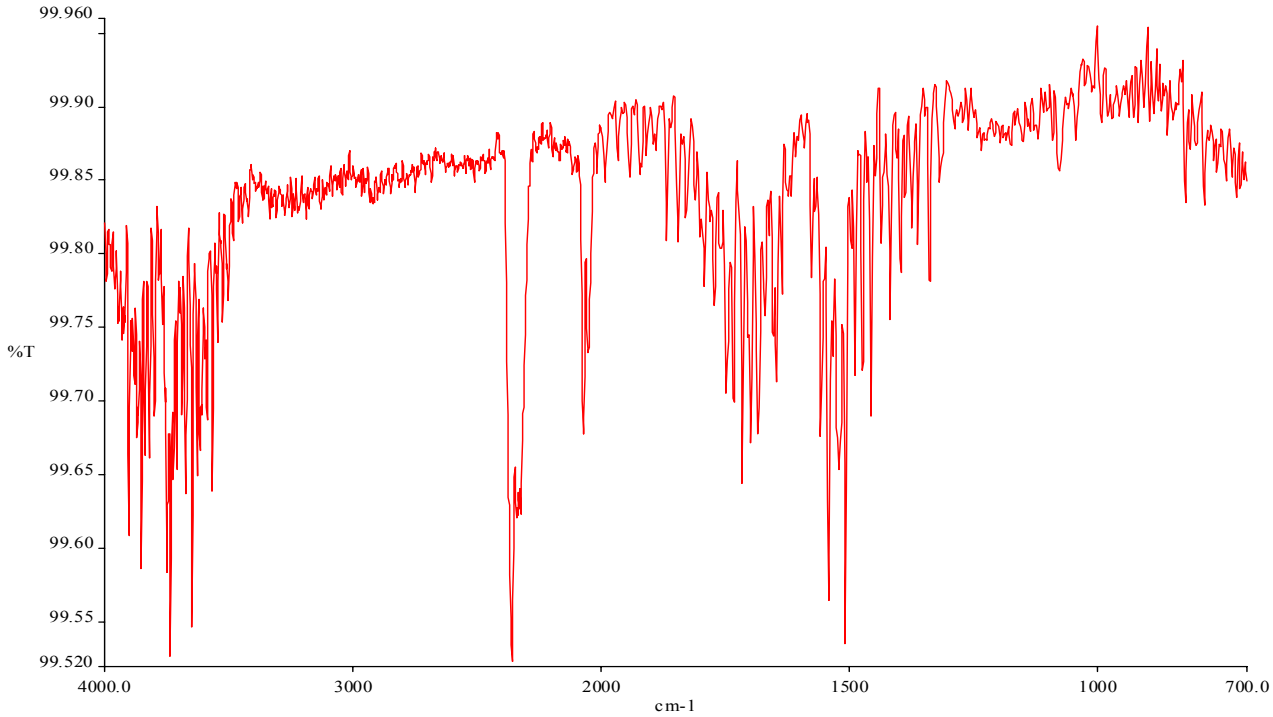
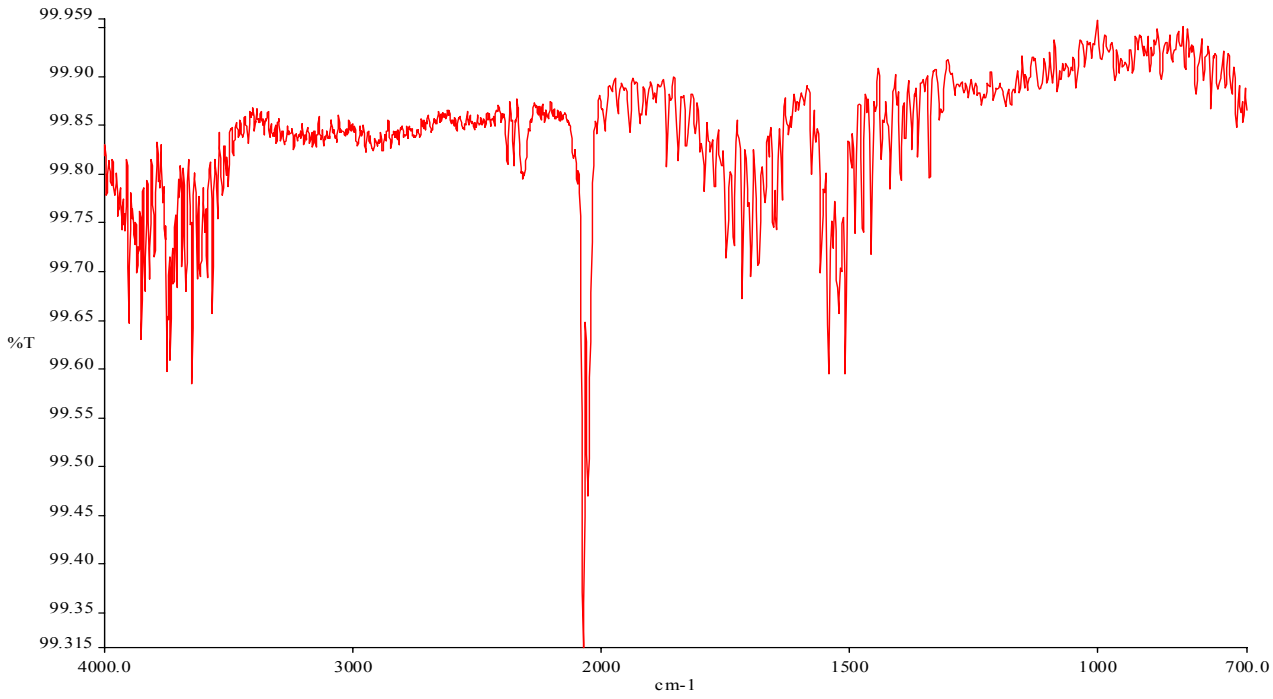


Fig. 4 – Thermoanalytical curves for cefoperazone monohydrate β= 20°C·min^{-1}.



a) Spectrum at 10.2 Mins (cefoperazone_EGA.spp).sp / Spectrum.lst Euclidean Search Hit List



b) Spectrum at 10.9 Mins (cefoperazone_EGA.spp).sp / Spectrum.lst Euclidean Search Hit List

Fig. 5 – FTIR spectra of gaseous mixtures observed above cefoperazone in air at a) 200°C and b) 215°C measured by the online TG–FTIR system (initial sample mass: 2.879 mg, heating rate: 20°C·min^{-1}).

Similarity of the EGA spectra is observed throughout the analysed process; the wave numbers are identical and they characterize the existence of the same compounds which result from total breakdown of the initial active substance, cefoperazone. The compounds that can be identified from the EGA spectra are: water vapours (ν=3750–3500 and 1900–1300 cm^{-1}); carbon dioxide (ν=2300–2250 and 750–600 cm^{-1}); carbon sulphide (ν=750–700 cm^{-1}); ethyl-

formamide (ν=1680–1660 cm^{-1} – stretching vibration C=O from amide; 1560–1530 cm^{-1} – stretching vibration N–H, respectively C–N); azine (ν=1615–1565 cm^{-1} – stretching vibration of C=N bond from aromatic cycle); phenol (ν=3550–3500 cm^{-1} – stretching vibration of O–H phenolic bond).

These products made out from the EGA spectra are according with the active substance's skeleton and are demonstrating a significant destruction of dihydrothiazine ring, but also of this ring's substituents, which are more bulky compared with the corresponding active substances substituents from the same class. IR spectra of cefoperazone–active substance before heat treatment are presented in Fig.6, and those after heat treatment in Fig.7 (Spectrum 100 Perkin Elmer device).

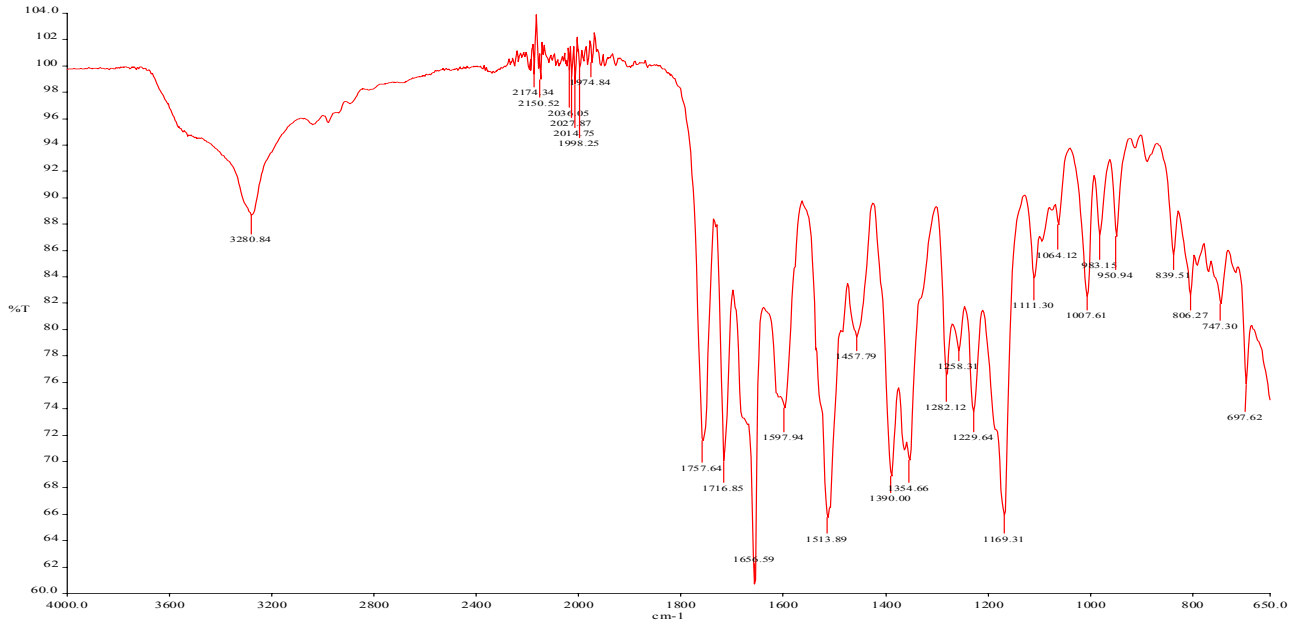


Fig. 6 – Infrared spectrum (FTIR) of cefoperazone monohydrate – before heat treatment.

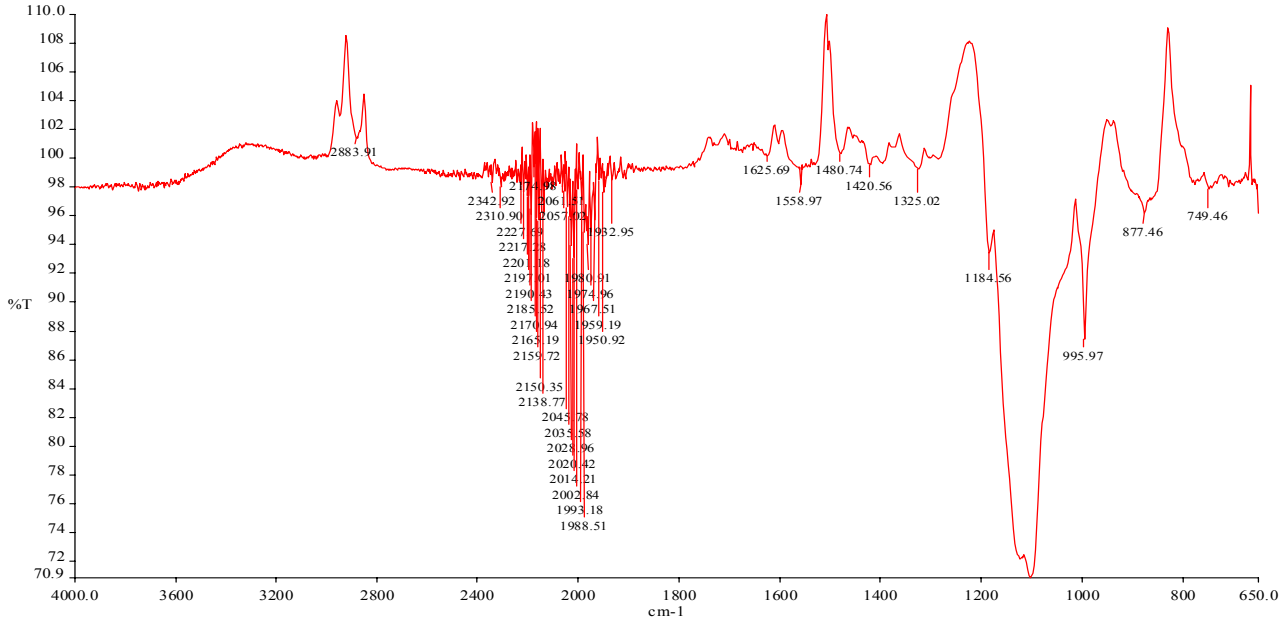


Fig. 7 – Infrared spectrum (FTIR) of cefoperazone monohydrate –after heat treatment at 550°C.

After the comparison of the FTIR spectra of the cefoperazone before and after heat treatment, one can observe the disappearing of the 3450 cm^{-1} band, that corresponding to the hydration water, the disappearing of those from the 1050–1200 cm^{-1} range, characteristic to the *β*–lactamic cycles, and

also the disappearing of those from the 1900–2170 cm^{-1} range corresponding to the heteroatom–hydrogen bonding and of those which underline the carbonyl and carboxyl groups (ν = 1760; 1690 cm^{-1}), which corresponds to the volatile products identified through EGA. [18–20]

EXPERIMENTAL

The cefoperazone (6R,7R)–7–[[2–[(4–ethyl–2,3–dioxopiperazine–1–carbonyl)amino]–2–(4–hydroxy-phenyl)acetyl]amino]–3–[(1–methyltetrazol–5–yl)sulfanylmethyl]–8–oxo–5–thia–1–azabicyclo[4.2.0]oct–2–ene–2–carboxylic acid was obtained from Antibiotice Iaşi – Roumania (lot: 01061164/580513–08471).

Thermogravimetrical analysis (TG and DTG) was performed on Perkin–Elmer DIAMOND equipment in temperature range 25–550°C, using an air atmosphere and under dynamic conditions in order to study the thermal stability of the active substance. Samples with the mass in the range of 2 to 5 mg were put into aluminium crucibles, at a heating rate, β, of 5, 7, 10 and 12°C·min^{-1}.

The evolved gas analysis (EGA) was carried out by a coupled TG/FTIR technique, using a Perkin Elmer SPECTRUM 100 devices with an IR gas chamber connected to the exit of the DIAMOND furnace. The same air flow of 100 mL·min^{-1} and a heating rate of 20°C·min^{-1} were used. The FTIR spectra were processed by the Sadtler Gas Vapor Library.

CONCLUSIONS

The investigated substance is stable up to 40°C in air. The combination of the complementary TG/FTIR technique provides a versatile and complete analytical system for the identification of gases evolved during thermal decomposition processes, respectively can provide precise time and/or temperature dependent on gas evolution information.

Cefoperazone monohydrate decomposes in three stages: evolution of weakly bound water molecule (dehydration process); releasing of carbon dioxide and ammonia with opening of cephem ring obtaining carbonyl sulphide and sulphur dioxide (connected with degradation of dihydrothiazine ring), respectively further decomposition with releasing of phenol, azine and N-ethyl-formamide from the substituent's thermal decomposition.

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